

The Claims

1. (Currently Amended) An apparatus comprising:
one or more processors; and
a memory coupled to the processors comprising one or more instructions, the processors operable when executing the instructions to:

determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex, the protein-ligand atom pair comprising a protein atom and a ligand atom, the protein atom comprising a first element and having a first local bonding environment that comprises the ligand atom, the ligand atom comprising a second element and having a second local bonding environment that comprises the protein atom, the atom-pair type being defined by the first and second elements and the combination of local bonding environments, the first and second local bonding environments each comprising:

a polar aliphatic bonding environment;

a nonpolar aliphatic bonding environment;

a polar aromatic bonding environment;

a nonpolar aromatic bonding environment;

a hydrogen bond donor bonding environment; or

a hydrogen bond acceptor bonding environment;

determine a minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

determine a well-depth value for the protein-ligand atom pair based on the atom-pair type, the well-depth value representing an amount of binding interaction for the atom-pair type;

~~generate a first set and at least a second set of empirically derived parameters, each set including a minimum binding energy distance value and a well depth value of the atom-pair type;~~

~~calculate a first and second repulsion term for of the protein-ligand atom pair based on the minimum binding-energy distance and well-depth values according to the first and second sets of empirically derived minimum binding-energy distance and well-depth values, respectively;~~

~~calculate a first and second potential of mean force (PMF) for of the protein-ligand atom pair in a predetermined repulsive region based on the repulsion term according to the calculated first and second repulsion terms, respectively, of the protein-ligand atom pair; and~~

~~calculate a first and second PMF score for of the protein-ligand complex based on the PMF, the PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex according to the calculated first and second PMF of the protein-ligand atom pair, respectively, each PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex;~~

~~predict first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;~~

~~calculate a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;~~

~~calculate a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;~~

~~determine agreement between the first set of empirically derived minimum binding-energy distance and well depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;~~

~~determine agreement between the second set of empirically derived minimum binding-energy distance and well depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and~~

~~communicate at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format.~~

2-8 (Canceled)

9. (Currently Amended) The apparatus of Claim 1, wherein one or more of the ~~first set of empirically derived~~ minimum binding-energy distance and well-depth values ~~or second sets of empirically derived minimum binding-energy distance and well-depth values~~ are each a product of one or more manual processes or automatic processes.

10. (Previously Presented) The apparatus of Claim 9, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

11. (Currently Amended) A method comprising:
determining, by one or more computer systems, an atom-pair type of a protein-ligand atom pair in a protein-ligand complex, the protein-ligand atom pair comprising a protein atom and a ligand atom, the protein atom comprising a first element and having a first local bonding environment that comprises the ligand atom, the ligand atom comprising a second element and having a second local bonding environment that comprises the protein atom, the atom-pair type being defined by the first and second elements and the combination of local bonding environments, the first and second local bonding environments each comprising:

a polar aliphatic bonding environment;

a nonpolar aliphatic bonding environment;

a polar aromatic bonding environment;

a nonpolar aromatic bonding environment;

a hydrogen bond donor bonding environment; or

a hydrogen bond acceptor bonding environment;

determining, by the one or more computer systems, a minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

determining, by the one or more computer systems, a well-depth value for the protein-ligand atom pair based on the atom-pair type, the well-depth value representing an amount of binding interaction for the atom-pair type;

~~generating a first set and at least a second set of empirically derived parameters, each set including a minimum binding energy distance value and a well depth value of the atom-pair type;~~

calculating, by the one or more computer systems, a first and second repulsion term for of the protein-ligand atom pair based on the minimum binding-energy distance and well-depth values according to the first and second sets of empirically derived minimum binding energy distance and well depth values, respectively;

calculating, by the one or more computer systems, a first and second potential of mean force (PMF) for of the protein-ligand atom pair in a predetermined repulsive region based on the repulsion term according to the calculated first and second repulsion terms, respectively of the protein-ligand atom pair; and

calculating, by the one or more computer systems, a first and second PMF score for of the protein-ligand complex based on the PMF, the PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex according to the calculated first and second PMF of the protein ligand atom pair, respectively, each PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex;

~~predicting first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;~~

~~calculating a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;~~

~~calculating a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;~~

~~determining agreement between the first set of empirically derived minimum binding-energy distance and well depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;~~

~~determining agreement between the second set of empirically derived minimum binding-energy distance and well depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and~~

~~communicating at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format.~~

12-18 (Canceled)

19. (Currently Amended) The method of Claim 11, wherein one or more of the ~~first set of empirically derived~~ minimum binding-energy distance and well-depth values ~~or second sets of empirically derived minimum binding-energy distance and well-depth values~~ are each a product of one or more manual processes or automatic processes.

20. (Previously Presented) The method of Claim 19, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

21. (Currently Amended) Software encoded in one or more computer-readable ~~tangible~~ storage media and when executed operable to:

determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex, the protein-ligand atom pair comprising a protein atom and a ligand atom, the protein atom comprising a first element and having a first local bonding environment that comprises the ligand atom, the ligand atom comprising a second element and having a second local bonding environment that comprises the protein atom, the atom-pair type being defined by the first and second elements and the combination of local bonding environments, the first and second local bonding environments each comprising:

a polar aliphatic bonding environment;

a nonpolar aliphatic bonding environment;

a polar aromatic bonding environment;

a nonpolar aromatic bonding environment;

a hydrogen bond donor bonding environment; or

a hydrogen bond acceptor bonding environment;

determine a minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

determine a well-depth value for the protein-ligand atom pair based on the atom-pair type, the well-depth value representing an amount of binding interaction for the atom-pair type;

~~generate a first set and at least a second set of empirically derived parameters, each set including a minimum binding energy distance value and a well depth value of the atom pair type;~~

~~calculate a first and second repulsion term for of the protein-ligand atom pair based on the minimum binding-energy distance and well-depth values according to the first and second sets of empirically derived minimum binding energy distance and well depth values, respectively;~~

~~calculate a first and second potential of mean force (PMF) for of the protein-ligand atom pair in a predetermined repulsive region based on the repulsion term according to the calculated first and second repulsion terms, respectively, of the protein-ligand atom pair; and~~

~~calculate a first and second PMF score for of the protein-ligand complex based on the PMF, the PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex according to the calculated first and second PMF of the protein-ligand atom pair, respectively, each PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex;~~

~~predict first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;~~

~~calculate a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;~~

~~calculate a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;~~

~~determine agreement between the first set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;~~

~~determine agreement between the second set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and~~

~~communicate at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user-readable format.~~

22-28 (Canceled)

29. (Currently Amended) The software of Claim 21 ~~Claim 25~~, wherein one or more of the ~~first set of empirically derived minimum binding-energy distance and well-depth values or second sets of empirically derived minimum binding-energy distance and well-depth values~~ are each a product of one or more manual processes or automatic processes.

30. (Previously Presented) The software of Claim 29, wherein at least one of the automatic processes comprises execution of a genetic algorithm.

31. (Currently Amended) A system comprising:
means for determining an atom-pair type of a protein-ligand atom pair in a protein-ligand complex, the protein-ligand atom pair comprising a protein atom and a ligand atom, the protein atom comprising a first element and having a first local bonding environment that comprises the ligand atom, the ligand atom comprising a second element and having a second local bonding environment that comprises the protein atom, the atom-pair type being defined by the first and second elements and the combination of local bonding environments, the first and second local bonding environments each comprising:

a polar aliphatic bonding environment;

a nonpolar aliphatic bonding environment;

a polar aromatic bonding environment;

a nonpolar aromatic bonding environment;

a hydrogen bond donor bonding environment; or

a hydrogen bond acceptor bonding environment;

means for determining a minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

means for determining a well-depth value for the protein-ligand atom pair based on the atom-pair type, the well-depth value representing an amount of binding interaction for the atom-pair type;

~~means for generating a first set and at least a second set of empirically derived parameters, each set including a minimum binding energy distance value and a well depth value of the atom-pair type;~~

~~means for calculating a first and second repulsion term for of the protein-ligand atom pair based on the minimum binding-energy distance and well-depth values according to the first and second sets of empirically derived minimum binding energy distance and well depth values, respectively;~~

~~means for calculating a first and second potential of mean force (PMF) for of the protein-ligand atom pair in a predetermined repulsive region based on the repulsion term according to the calculated first and second repulsion terms, respectively of the protein-ligand atom pair; and~~

~~means for calculating a first and second PMF score for of the protein-ligand complex based on the PMF, the PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex according to the calculated first and second PMF of the protein-ligand atom pair, respectively, each PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex;~~

~~means for predicting first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;~~

~~means for calculating a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein ligand complex;~~

~~means for calculating a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;~~

~~means for determining agreement between the first set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom-pair based at least in part on the first RMS deviation;~~

~~means for determining agreement between the second set of empirically derived minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom-pair based at least in part on the second RMS deviation; and~~

~~means for communicating at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom-pair in a user-readable format.~~

32. (New) The system of Claim 1, wherein the minimum binding-energy distance value is an empirically derived value.

33. (New) The system of Claim 1, wherein the well-depth value is an empirically derived value.

34. (New) The system of Claim 1, wherein:
the minimum binding-energy distance and well-depth values are part of a first set of minimum binding-energy distance and well-depth values;
the calculated repulsion term represents a first repulsion term;
the calculated PMF represents a first PMF;
the calculated PMF score represents a first PMF score; and
the processors are further operable when executing the instructions to:
determine a second set of minimum binding-energy distance and well-depth values, the second set comprising:
at least a second minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the second minimum binding-

energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

at least a second well-depth value for the protein-ligand atom pair based on the atom-pair type, the second well-depth value representing an amount of binding interaction for the atom-pair type;

calculate a second repulsion term for the protein-ligand atom pair based on the second minimum binding-energy distance and second well-depth values;

calculate a second potential of mean force (PMF) of the protein-ligand atom pair based on the second repulsion term; and

calculate a second PMF score for the protein-ligand complex based on the second PMF, the second PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex .

35. (New) The system of Claim 34, wherein the processors are further operable when executing the instructions to:

predict first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;

calculate a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;

calculate a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;

determine agreement between the first set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;

determine agreement between the second set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and

communicate at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format.

36. (New) The method of Claim 11, wherein the minimum binding-energy distance value is an empirically derived value.

37. (New) The method of Claim 11, wherein the well-depth value is an empirically derived value.

38. (New) The method of Claim 11, wherein:
the minimum binding-energy distance and well-depth values are part of a first set of minimum binding-energy distance and well-depth values;
the calculated repulsion term represents a first repulsion term;
the calculated PMF represents a first PMF;
the calculated PMF score represents a first PMF score; and
the method further comprises:
determining a second set of minimum binding-energy distance and well-depth values, the second set comprising:
at least a second minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the second minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;
at least a second well-depth value for the protein-ligand atom pair based on the atom-pair type, the second well-depth value representing an amount of binding interaction for the atom-pair type;
calculating a second repulsion term for the protein-ligand atom pair based on the second minimum binding-energy distance and second well-depth values;
calculating a second potential of mean force (PMF) of the protein-ligand atom pair based on the second repulsion term; and

calculating a second PMF score for the protein-ligand complex based on the second PMF, the second PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex .

39. (New) The method of Claim 38, further comprising:
- predicting first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;
 - calculating a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;
 - calculating a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;
 - determining agreement between the first set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;
 - determining agreement between the second set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and
 - communicating at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format.

40. (New) The software of Claim 21, wherein the minimum binding-energy distance value is an empirically derived value.

41. (New) The software of Claim 21, wherein the well-depth value is an empirically derived value.

42. (New) The software of Claim 21, wherein:

- the minimum binding-energy distance and well-depth values are part of a first set of minimum binding-energy distance and well-depth values;

the calculated repulsion term represents a first repulsion term;

the calculated PMF represents a first PMF;

the calculated PMF score represents a first PMF score; and

the software is further operable when executed to:

determine a second set of minimum binding-energy distance and well-depth values, the second set comprising:

at least a second minimum binding-energy distance value for the protein-ligand atom pair based on the atom-pair type, the second minimum binding-energy distance value representing a distance corresponding to a minimum binding-energy for the atom-pair type;

at least a second well-depth value for the protein-ligand atom pair based on the atom-pair type, the second well-depth value representing an amount of binding interaction for the atom-pair type;

calculate a second repulsion term for the protein-ligand atom pair based on the second minimum binding-energy distance and second well-depth values;

calculate a second potential of mean force (PMF) of the protein-ligand atom pair based on the second repulsion term; and

calculate a second PMF score for the protein-ligand complex based on the second PMF, the second PMF score indicating a binding affinity between the protein and ligand in the protein-ligand complex .

43. (New) The software of Claim 42, wherein the software is further operable when executed to:

predict first and second structures of the protein-ligand complex according to the first and second PMF scores, respectively;

calculate a first root mean square (RMS) deviation between the first predicted structure and an actual, analyzed structure of the protein-ligand complex;

calculate a second root mean square (RMS) deviation between the second predicted structure and the actual, analyzed structure of the protein-ligand complex;

determine agreement between the first set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the first RMS deviation;

determine agreement between the second set of minimum binding-energy distance and well-depth values and the actual, analyzed protein-ligand atom pair based at least in part on the second RMS deviation; and

communicate at least the PMF score from the first and second PMF scores that is in best agreement with the actual, analyzed protein-ligand atom pair in a user readable format.